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Compliance with inhaled glucocorticoids and concomitant use of long-acting β_2-agonists

H. J. VAN DER WOUDE AND R. AALBERS

Department of Pulmonology, Martini Hospital, Groningen, The Netherlands

We investigated whether treatment with a long-acting β_2-agonist (LAβ_2) is associated with a decrease in patient compliance with regard to inhalation corticosteroids (ICS).

Date on prescriptions collected by 15 760 patients suffering from airways disease were provided by 69 Dutch pharmacies. All prescriptions of ICS and LAβ_2 were analysed and divided in four groups by LAβ_2 use during 1997 and 1998.

Date from 15 760 patients were available. In the 10 929 patients not treated with LAβ_2, compliance decreased slightly but not significantly. In 3281 patients receiving LAβ_2 compliance also decreased slightly but not significantly. In 404 patients, who used a LAβ_2 in 1997 and discontinued treatment in 1998, the compliance fell significantly ($P<0{\cdot}05$). In 1147 patients who started to use a LAβ_2 in 1998, compliance with ICS significantly improved ($P<0{\cdot}05$).

These results suggest that the regular use of LAβ_2 improves compliance with ICS. Therefore, the concern that compliance with inhaled corticosteroid therapy will decrease under concomitant use of LAβ_2 appear to be unfounded.

Key words: inhalation steroid; compliance; long-acting β_2-agonists.

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Introduction

In the early 1990s, the treatment of asthma and chronic obstructive pulmonary disease (COPD) significantly changed following the introduction of the long-acting β_2-agonists (LAβ_2) salmeterol and formoterol. However, monotherapy with short-acting as well as long-acting β_2-agonists is not recommended because this may be associated with a relative under-treatment, and in addition mask the disease's underlying inflammatory process (1,2). International standards (3) only recommend maintenance treatment with LAβ_2 in conjunction with inhaled glucocorticosteroid (ICS).

The rapid relief of asthma symptoms provided by LAβ_2 clearly contrasts with the action of ICS. However, as ICS are now accepted as the foundation for asthma treatment, the concomitant use of LAβ_2 with their high subjective efficacy may jeopardize compliance with ICS usage. This prompted us to investigate whether the compliance with ICS will change when a patient concomitantly uses a LAβ_2. The hypothesis tested was that after the initiation of the subjectively strong-acting LAβ_2 the compliance with ICS might decrease.

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Correspondence should be addressed to: Dr R. Aalbers, Department of Pulmonology, Martini Hospital (Van Swieten site), Van Swietenlaan 4, 9728 NZ Groningen, The Netherlands. Fax: +31 (0) 50 5245937.

Methods

Electronic prescription data from 69 pharmacies across The Netherlands were obtained from patients who collected at least two prescriptions for an ICS in 1997 and 1998. Compliance with ICS use was calculated by dividing the anticipated interval from the prescribed dose and the actual interval between collecting the subsequent prescriptions. The population was divided into four groups to compare compliance with ICS during these 2 years. The first group, group A, contained the so-called 'starters'. These patients did not receive a prescription for LAβ_2 in 1997 but received at least one in 1998. The second group, group B ('never-users'), contained those patients who never concomitantly used LAβ_2 in 1997 and 1998. The third group, group C, contained patients who are using ICS and LAβ_2 in 1997 as well as in 1998. This group is called the 'ever-users'. The last group, group D ('stoppers'), used LAβ_2 at least once in 1997 but never in 1998. The patients' characteristics are presented in Table 1.

STATISTICS

The results of demographics and compliance are expressed as both mean ± standard deviation (SD) and median values. The main objective was the compliance of inhaled steroid use during 1997 and 1998. Data from 1997 were compared with data from 1998 using a paired Student's *t*-test for normally distributed data (two-tailed) and the Wilcoxon-

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TABLE 1. Demographic data and compliance with ICS and LAβ_2 use of 15 760 patients, collected in 69 Dutch pharmacies. The division is by the concomitant LAβ_2 use during 1997 and/or 1998

		Group A (starters)	Group B (never-users)	Group C (even-user)	Group D (stoppers)
Number of patients		1146	10 929	3281	404
% male		48·3%	47·9%	52·4%	44·7%
Age (years ±SD)		52·1±22·5	43·9±25·8	54·2±21·0	46·8±23·4
Amount of ICS-receipts/patient	1997	2·2	2·6	2·8	2·6
	1998	2·6	2·6	2·9	2·5
Receipt duration (days)	1997	74·6	76·5	76·5	77·2
	1998	78·0	82·6	79·2	74·4
Daily dosage ICS ($\mu g\,day^{-1}$)	1997	791	676	906	812
	1998	776	682	900	832
Compliance with ICS (%)	1997	103·1	100·0	104·7	109·9
	1998	106·4*	98·9	102·0	102·0*
Compliance with LAβ_2 (%)	1997	–	–	102·0	94·5
	1998	101·2	–	100·0	–

ICS: inhalation glucocorticosteroid; LAβ_2: long-acting β_2-agonist.
For almost all data: mean value±standard deviation (SD), for compliance median values.*$P<0{\cdot}05$, *t*-test.

rank test for non-normally distributed data. A *P*-value less than 0·05 was considered significant.

Results

Data from 15 760 patients were available, divided into four groups by their LAβ_2 use during 1997 and/or 1998 as shown in Table 1. No great dissimilarities between the groups were observed.

The prescribed medication, the expected and real interval between two ICS prescriptions, as well as calculated compliance, are shown in Table 1. Multiple inhalers could be prescribed on one receipt. The median compliance with ICS is presented in Fig. 1, and is remarkably high in all four groups (close to 100%). The compliance decreased in three groups from 1997 to 1998 whereas in group A, patients who started to use LAβ_2 on top of their ICS, compliance for ICS increased. In groups A and D, changes in compliance are statistically significant ($P<0{\cdot}05$). In groups B and C no change in compliance was observed. The compliance for LAβ_2 in 1997 and 1998 are similar (Table 1).

The daily dosage of ICS remained stable during the observed period. The dosage of ICS was highest in group C, the patients who used a LAβ_2 in 1997 and 1998. The lowest dose of ICS was used by the patients in group B, the never-users. In groups A and D the daily dosage of ICS did not significantly increase.

Discussion

We tested the hypothesis that after the initiation of the subjectively strong-acting LAβ_2 the compliance with ICS may decrease. However, compliance with ICS improved significantly after the start of LAβ_2 and attenuated if the LAβ_2 was stopped. In the groups without concomitant LAβ_2 use or with continuation of use of LAβ_2, compliance with ICS remained the same.

A probable explanation for the present findings is that compliance with ICS is boosted by the highly subjective efficacy of the LAβ_2. The effect of LAβ_2 is easily recognized by patients, and gives an improvement of the lung function and relief of symptoms within days in contrast to the effects of ICS, which are only measurable after weeks and may go unnoticed by the patient. As these effects are not easily recognized by patients, compliance with the medication may be hindered. It could be that the patient's trust in the efficacy of prescribed medication may improve, if a subjectively strong-working medication is combined with a subjectively less effective medication. However, this idea has never been proved.

In this study prescription data of delivered medication from a large group of patients who received at least two prescriptions for ICS are analysed. This excludes patients with poor compliance, patients who only need medication for a short period (for example patients suffering from seasonal asthma) and patients who do not fetch their prescribed medication [about 10% of the population (4)]. From the latter group one may doubt if this would have influenced the results of this study: because if patients are not willing to fetch their prescribed medication, the addition of long-acting β_2-agonists will presumably not alter the compliance of inhaled steroids.

However, although a correct timing of prescription renewal is suggestive for correct adherence to prescribed treatment, this is not certain. In clinical trials, for instance, about one in three of the patients 'cheats' in this way (5). Indeed, during a clinical trial patients are aware of being observed which may induce sociably desired behaviour and

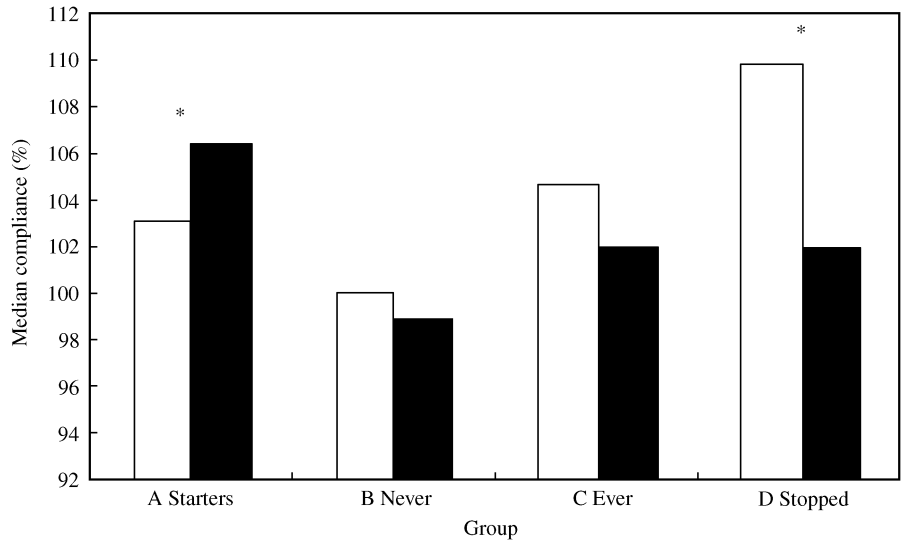

FIG. 1. Compliance (%, median value) with inhaled glucocrticosteroid therapy. Group A: started with the use of LAβ_2 in 1998 ($n = 1446$); group B: no concomitant use of LAβ2 in both 1997 and 1998 ($n = 10\,929$); group C: in both years concomitant LAβ2 use ($n = 3281$); group D: the concomitant use of LAβ2 is stopped in 1998 ($n = 404$). *$P < 0{\cdot}05$. 1997 (open bars), 1998 (solid bars).

so fetching the prescribed medication in time. In our study, patients were unaware of being observed leading to a more natural pattern of behaviour.

Several other methods are available for measuring compliance, such as biochemical measures, clinical judgement, self-report, asthma diaries and medication monitors. These methods may be more accurate but have other disadvantages which limit their use on a large scale. Biochemical measures are invasive, expensive and provide no information about usage patterns over time (6). Clinical judgement had a low validity and reliability (6). Self-report and diaries have a highly variable validity (6). Diaries are vulnerable to patients' deceit (6). Medication monitors are expensive and patients can react to the presence of a monitoring device.

Examining pharmacy records of dispensing patterns is regarded as useful for measuring compliance with long-term medication regimens (6) and has proven to be useful in investigating trends or hypotheses (7). It is an unobtrusive method, as neither the patients nor the physicians are aware of the registration process. Accordingly there is no interference with the natural patterns of medication use and the bias within the study is therefore reduced. It provides only a course estimation of compliance and probably over-estimates it, since neither the return of medication nor the daily pattern of medication use and adherence is monitored (6). Thus, this methods is valid for examining trends in patients using chronically ICS and LAβ_2 and the present study is unique with respect to the large number of patients (25 000). According to this study, the concomittant use of LAβ_2 does not decrease compliance in patients who chronically use ICS.

The results of this study are confirmed by a recent using prescribed data instead of delivered medication (4). An increase in compliance with ICS from 90% to 103% on the addition of LAβ_2 was observed. Also, in other studies the addition of salmeterol (8) or short-acting β_2 (9) did not adversely affect compliance with inhaled corticosteroid therapy (7).

A remarkable finding of our study is that physicians, until now, do not lower the dose of ICS when additional LAβ_2 is prescribed. This is in contrast to the recently published studies which show that adding LAβ_2 to ICS therapy is as effective or even more effective than increasing the ICS dose two- to four-fold (10–12).

In summary, the results of our study show no decrease in compliance with ICS when LAβ_2 is added in patients who chronically use inhaled corticosteroids. On the contrary, LAβ_2 improves compliance with ICS.

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